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Research paper

The diagnostic value of continuous EEG for the detection of non-convulsive status epilepticus in neurosurgical patients – A prospective cohort study

Thomas Krøigård [a,e,*], Axel Forsse [b,e], Karsten Bülow [c], Jesper Broesby [c], Frantz R. Poulsen [b,e], Troels W. Kjaer [d,f], Hans Høgenhaven [a]

[a] Department of Neurology, Odense University Hospital, Denmark
[b] Department of Neurosurgery, Odense University Hospital, Denmark and BRIDGE Brain Research – Inter Disciplinary Guided Excellence, Denmark
[c] Department of Anaesthesiology and Intensive Care, Odense University Hospital, Denmark
[d] Department of Neurophysiology, Zealand University Hospital, Denmark
[e] Department of Clinical Research, University of Southern Denmark, Denmark
[f] Department of Clinical Medicine, University of Copenhagen, Denmark

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ABSTRACT

Objective: To prospectively compare the diagnostic yields of standard EEG and continuous EEG (cEEG) monitoring for the diagnosis of non-convulsive status epilepticus (NCSE) in neurosurgical patients in the intensive care unit.
Methods: We included 50 consecutive patients with clinical suspicion of NCSE due to unexplained coma or subtle clinical phenomena such as discrete myoclonus. The initial 30-minute EEG recording and the following cEEG were analyzed separately for seizure activity. Data were collected on neurosurgical diagnosis, previous diagnosis of epilepsy, current medication, level of consciousness, and outcome at discharge from the neurosurgical department.
Results: Recurrent electrographic seizure activity was detected in five patients. This was within the first 30 mins for three patients and on the following cEEG for two patients. Antiepileptic treatment had been initiated in three of these patients. Most of the 50 patients had severe newly acquired neurological disability at discharge.
Conclusions: The prospective finding of a 10% seizure incidence was lower than reports from retrospective studies.
Significance: Use of cEEG led to detection of seizure activity in 2 of 50 patients (4%) and was thus a low-yield method in neurosurgical patients with suspicion of NCSE. Specific markers for patient selection for cEEG are needed.

1. Introduction

Critically ill patients with unexplained coma use a substantial proportion of the clinical resources in neurointensive care units due to prolonged need for mechanical ventilation and extensive diagnostic work-up. Non-convulsive status epilepticus (NCSE) or non-convulsive seizures (NCSz) may be the sole factor or a contributing factor to coma in these patients. Rapid diagnosis and treatment could shorten the duration of coma and improve long-term outcome. Among patients in intensive care units, seizures (mostly non-convulsive) have been reported in 22–33% after traumatic brain injury, 3–26% after subarachnoid hemorrhage, and 3–17% after intracerebral hemorrhage (Claassen et al., 2013).

NCSE and NCSz are diagnosed by electroencephalography (EEG), traditionally performed for 30 min. However, retrospective studies of continuous EEG monitoring (cEEG) over one or several days indicate that electrographic seizure activity can occur later than 30 min after initiation of recording. In a study of 570 patients with reduced level of consciousness due to various etiologies, 19% had electrographic seizures and in 44% of these, seizures occurred more than one hour after initiation of recording (Claassen et al., 2004).

* Corresponding author at: Department of Neurology, Odense University Hospital, Department of Clinical Research, University of Southern Denmark, J. B. Winsløws Vej 4, 5000 Odense C, Denmark.
E-mail address: Thomas.Kroigard@rsyd.dk (T. Krøigård).

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Risk factors for seizures included a history of epilepsy, recent neurosurgical procedure, and convulsive seizures prior to monitoring. Similarly, Westover et al. (2015) reported that 27% of 625 patients had seizures and in 42% of these patients, the seizures occurred after 30 min. Seizures were associated with subdural hematoma and hypoxic ischemic encephalopathy.

The aim of the present study was to prospectively compare the diagnostic yields of 30-minute EEG recording and continuous EEG over a minimum of 18 h (cEEG) for the detection of seizure activity. We focused on a well-characterized population of neurosurgical intensive care patients with unexplained reduced level of consciousness or clinical suspicion of NCSE.

2. Methods

We included 50 consecutive patients who were admitted to the neurointensive care unit at Odense University Hospital and referred for acute EEG between January 1, 2016 and March 26, 2018. Inclusion criteria were 1) reduced level of consciousness not explained by known cerebral lesions, drugs or other medical conditions, and 2) clinical suspicion of NCSE due to observations such as discrete myoclonus.

Video-EEGs were recorded using a NicoletOne Neurodiagnostic system (Natus Neurology, Middleton, USA) according to the international 10–20 system. The EEG was analyzed in two separate steps. The initial 30 min of the recording were analyzed immediately, and seizure activity was noted. This part of the recording was described by EEG examiners HH or TK according to current standard reporting of acute 30-minute EEGs, and the conclusion was communicated to the treating physician. The rest of the recording, which had a duration of at least 18 h, was analyzed on the following day, and findings were reported to the clinician. Only unequivocal seizure activity lasting at least 10 s and fulfilling the Salzburg consensus criteria (Beniczky et al., 2013) was included in the analysis. The entire EEG recording was inspected, and appropriate trends analysis was applied using the NicoletOne v5.94.1.534 software. Lateralized periodic discharges (LPDs) and diffuse slowing of the EEG were also noted. Patients were only included four days a week (Monday to Thursday) as EEG evaluators were not available for EEG analysis at weekends.

Data were collected on neurosurgical diagnosis, previous diagnosis of epilepsy, current medication, level of consciousness assessed using the Glasgow Coma Score and the Richmond Agitation-Sedation Scale (Sessler et al., 2002), semiology, and neurological status according to the modified Rankin Score (mRS) (van Swieten et al., 1988) (Table 1) at the time of discharge from the Department of Neurosurgery.

The study was approved by the Health Research Ethics Committee for the Region of Southern Denmark (case ref. S-20150099) and the Danish Data Protection Agency (case ref. 15/38639). Written informed consent was obtained from patients' relatives at the time of inclusion. In cases where the patient later regained consciousness, informed consent was also obtained from the patient. None of the included patients refused to participate or later withdrew their consent.

Table 1
The modified Rankin Score (mRS).

mRS	Neurological status
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead.

3. Results

Patient characteristics are presented in Table 2. Most were males (70%), and 22% had alcohol abuse. Only three patients (6%) had prior epilepsy. The most frequent diagnoses were spontaneous subarachnoid hemorrhage (26%), spontaneous intracerebral hemorrhage (20%), and acute traumatic subarachnoid hemorrhage (18%).

Continuous EEG monitoring was performed in all included patients but was prematurely discontinued in one patient due to acute surgical intervention. Median duration of cEEG monitoring was 19 h (range 12–24 h). During recording, 46% of patients were treated with the sedatives propofol, midazolam, or a combination of these (Table 3). Antiepileptic medication had been initiated before recording in 34% of patients. Levetiracetam was the most frequently used antiepileptic drug, administered to 20% of patients as monotherapy and to 12% in combination with other antiepileptic drugs. Patients had severely depressed level of consciousness evaluated by the Glasgow Coma Score and Richmond Agitation-Sedation Scale (Table 4). The most frequently observed semiology prior to recording was abnormal motor activity described as "shivering" in 34% of patients. However, semiology such as clonic (10%) or tonic-clonic seizures (12%) was also noted.

Electrographic seizure activity was observed in five patients, LPDs in two patients, and encephalopathy not explained by medication in ten patients. Findings in patients with seizure activity are presented in Table 5.

NCSE or repeated seizure activity was detected within the first 30 min of recording in three patients (6%) and after 30 min in two patients (4%). Seizure activity occurred with relatively stable intervals, as indicated in Table 5, but varied in intensity (amplitude) and topographic localization. When the EEGs of the two patients with seizure activity identified after 30 min were reviewed retrospectively, extremely subtle electrographic seizure activity could also be seen during the first 30 min of recording.

Antiepileptic treatment was intensified in all patients with seizure activity in the EEG. The treatment response in patients with detectable seizure activity within and after 30 min could not be compared directly as treatment was intensified either after evaluation of the first 30 min of EEG or on the following day. Clinical outcome at discharge was generally poor for patients with seizure

Table 2
Patient characteristics.

Age, median (range)	61 (18–87)
Sex, male/female	35/15
Alcohol abuse (patients)	11
Epilepsy prior to admission (patients)	3
Diagnosis (patients (n = 50))	
Spontaneous SAH	13
Spontaneous ICH	10
Acute traumatic SDH	9
Traumatic ICH	6
Chronic traumatic SDH	3
Postoperative complications	4
Epidural hematoma	1
Traumatic brain injury	1
Venous sinus thrombosis	1
Cerebellar infarction	1
Acute hydrocephalus	1
mRS at discharge, median (range)	5 (2–6)

ICH: Intracerebral hemorrhage; mRS: Modified Rankin Score; SAH: Subarachnoid hemorrhage.

Table 3
Medication at initiation of recording.

Sedation	Patients (n = 50)
Propofol	9
Midazolam	4
Propofol and midazolam	10
Total	23
Antiepileptic medication	
Levetiracetam	10
Valproate	1
Levetiracetam and valproate	2
Levetiracetam and phenobarbital	2
Levetiracetam, valproate and lacosamide	1
Levetiracetam, valproate and phenytoin	1
Total	17

Table 4
Level of consciousness at initiation of EEG and semiology prior to EEG.

Level of consciousness	
GCS, median (range)	4 (3–15)
RASS, median (range)	−4 (−5–0)
Semiology prior to EEG (patients)	
"Shivering"	17
Clonic seizure	5
Generalized tonic-clonic seizure	4
Generalized tonic-clonic seizure and "shivering"	2
Tonic seizure	2
Tonic seizure and "shivering"	1
Paresis	1
"Abnormal behavior"	1
Automatism	1
Total	34

GCS: Glasgow Coma Score; RASS: Richmond Agitation-Sedation Scale.

activity (mRS 5–6), as it was for most of the patients in the study, but one patient had a more favorable outcome (mRS 2). Three of the patients with NCSE or repeated seizure activity had acute traumatic subdural hemorrhage, corresponding to 33% of the patient population.

4. Discussion

To our knowledge, this is the first prospectively conducted cohort study on the diagnostic yield of cEEG. We found a 10% incidence of electrographic NCSE or repeated seizure activity among 50 neurosurgical patients with clinical suspicion of NCSE. This incidence is approximately half that of electrographic seizures reported in large retrospective studies (Claassen et al., 2004; Westover et al., 2015). Two of our cases of NCSE were identified more than 30 min after initiation of EEG, which corresponds to the fraction found in the retrospective studies.

The relatively low incidence of NCSE in our study could be due to antiepileptic treatment being initiated prior to EEG in one-third of our patients on the basis of epileptiform semiology and a low threshold for instituting therapy among the neurointensivists. A retrospective study of electrographic seizures detected using cEEG in neurosurgical patients found a 22% incidence of subclinical seizures at a mean time of 2.8 h after EEG initiation but did not report the fraction of seizures within the first 30 min or whether seizures were recurrent (Freund et al., 2018). LPDs have previously been reported as an EEG marker of increased seizure risk (Claassen et al., 2004, Newey et al., 2017). This was not confirmed in the present study, probably due to a relatively small sample size. Two patients had LPDs, but none of them had seizures. Seizure risk was associated with lower levels of consciousness in a retrospective study aimed at identifying markers for a targeted cEEG monitoring approach (Newey et al., 2018). The average seizure risk was 19%, but even among awake patients 10% had seizures. In our population, all patients with seizures had impaired consciousness.

Most of our patients had a neurosurgical diagnosis associated with actual or potential severe brain damage. As a result, they had usually been sedated with midazolam or a combination of midazolam and propofol in both the acute and stabilization phases of neurointensive treatment, e.g. to stabilize intracranial pressure or for neuroprotection. Almost half the patients were still on sedative medication at the time of EEG recording, and the antiepileptic effect of especially midazolam may have reduced the seizure incidence. Patients were not monitored during the acute phase of neurointensive treatment, and the incidence of seizures may have been higher then despite sedation due to the acute cerebral damage.

Extremely discrete electrographic seizure activity was found in the initial 30 min of recordings in patients where the primary analysis revealed seizure activity only after 30 min. Future development of more sensitive automated seizure detection algorithms or trends analysis tools could increase the overall sensitivity for seizure detection, thereby reducing the need for cEEG. Under any circumstances, it is likely that seizure activity would need to recur after a shorter interval than 30 min to cause a significant reduction in the level of consciousness.

Although the examiners were not blinded, the major strength of our study is the prospective cohort design that ensured separate evaluation of the standard 30-minute EEG recording and the following cEEG. This improved the validity of the clinical data compared to previous retrospective studies. A limitation was that for practical reasons, we could not initiate EEG recording immediately after referral from the treating clinicians. This may have contributed to the relatively high proportion of patients on antiepileptic drugs prior to EEG and the low incidence of NCSE. From a practical standpoint, antiepileptic treatment with non-sedating antiepileptic drugs, such as levetiracetam, based on clinical suspi-

Table 5
Characteristics of patients with seizure activity.

Patient	Diagnosis	Seizure type	Seizure frequency	Detected at	AEDs before EEG	Intervention	Clinical outcome, mRS
1	atSDH	Focal tonic-clonic	1/10-15 min	Standard EEG	Levetiracetam	Seizure control after phenytoin during cEEG	2
2	atSDH	Focal, no clinical change	1/3-4 mins	Standard EEG	None	Seizure control after increased propofol during cEEG	5
3	atSDH	Focal clonic	1/10-15 mins	Standard EEG	None	Seizure control after levetiracetam during cEEG	6
4	sICH	Focal, no clinical change	1/2-3 mins	cEEG	Levetiracetam, phenobarbital	No seizure control despite increased sedation	5
5	aSAH (aneurysmal)	Focal clonic	1/20 mins	cEEG	Levetiracetam	No seizure control despite valproate	6

AEDs: Antiepileptic drugs; aSAH (aneurysmal): Acute spontaneous subarachnoid hemorrhage due to rupture of intracranial aneurysm; atSDH: Acute traumatic subdural hemorrhage; mRS: Modified Rankin Score; sICH: Spontaneous intracerebral hemorrhage.

cion alone may be a rational strategy to reduce the need for cEEG. The low incidence of serious side effects and the uncomplicated withdrawal of treatment once the patient is stabilized support this approach. Our median recording duration of 19 h is shorter than the 24–48 h of recording used by most neurophysiologists (Gavvala et al., 2014). However, since less than 5% of seizures occur more than 24 h after initiation of recording in the absence of epileptiform activity (Struck et al., 2017), this is unlikely to have affected our results significantly. We believe our defined study period would have identified all patients with NCSE.

At the time of discharge, four of the five patients with NCSE had a moderately severe or severe disability (mRS 5–6). The most important determinant for the clinical outcome after status epilepticus is etiology, and duration of status epilepticus was not associated with outcome after correction for confounding factors (Drislane et al., 2009). More research is needed to determine the influence of early seizure detection and treatment of NCSE on patient outcome.

We conclude that cEEG in neurosurgical patients with clinical suspicion of NCSE based on general criteria, such as reduced level of consciousness, is not indicated. Diagnostic clarification was reached within the first 30 min of EEG recording in 96% of patients. The most commonly observed semiology of "shivering" was not correlated to NCSE in our study and should not in itself be an indication for cEEG. However, epileptiform semiology such as discrete clonus and very epileptogenic neurosurgical conditions such as acute traumatic subdural hemorrhage should increase the suspicion of NCSE and may warrant cEEG monitoring. Although not examined in the present study, cEEG-monitoring has additional indications, such as evaluation of treatment effects in refractory status epilepticus.

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Declarations of interest

None of the authors have potential conflicts of interests to be disclosed.

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